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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,475	10/10/2001	Ryuichi Morishita	6235-59221	4309

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	16

DATE MAILED: 05/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,475	MORISHITA ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/4/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,11,12,14-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,11,12,14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 9, 11, 12, and 14-16 are pending examination.

The applicants' traversal, the amendment to the specification, the amendment to claims 9 and 14-16 and the cancellation of claims 1-8, 10, 13, 17-21 in paper no. 15 filed on 3/4/03 is acknowledged and considered.

Claim Objections

Applicants' arguments, see paper no. 15, filed on 3/4/03, with respect to the objection for claims 1 and 9 have been fully considered and are persuasive. The objection of claims 1 and 9 has been withdrawn because of the cancellation of claim 1 and the amendment to claim 9.

However, in view of the finality of the restriction in paper no. 12 mailed on 10/03/02, claim 11 is objected to because the claim reads on non-elected embodiment (diabetic ischemic neuropathy and diabetic ischemic myocardial infarction).

Claim Rejections - 35 USC § 112

Applicants' arguments, see paper no. 15, filed on 3/4/03, with respect to the 112 enablement rejection for claims 1-21 have been fully considered and are persuasive. The rejection of claims 1-21 has been withdrawn because of the cancellation of claims 1-8, 10, 13, and 17-21 and the amendment to claim 9.

Applicants' arguments, see paper no. 15, filed on 3/4/03, with respect to the 112 second paragraph rejection for claims 16-21 have been fully considered and are persuasive. The rejection of claims 16-21 has been withdrawn because of the cancellation of claims 17-21 and the amendment to claim 16.

Double Patenting

Applicants' arguments, see paper no. 15, filed on 3/4/03, with respect to the obviousness-type double patenting rejection for claims 1-7 have been fully considered and are persuasive because of the cancellation of claims 1-7.

Claim Rejections - 35 USC § 102

Applicants' arguments, see paper no. 15, filed 3/4/03, with respect to the rejection(s) of claim(s) 1-12 and 15-20 under 102 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn because of the cancellation of claims 1-8, 10, 13, and 17-21 and the amendment to claim 9. However, upon further consideration, a new ground(s) of rejection is made in view of Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 9, 11, 12, and 14-16 are rejected under 35 U.S.C. 102(e) as anticipated by Morishita et al. (US 6,248,722) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) (IDS). Morishita teaches a method of nucleic acid therapy for treating a disease in a subject for which hepatocyte growth factor (HGF) is effective, comprising administering to the muscle of the subject a HVJ-liposome comprising HGF (column 14). Morishita teaches that HGF can treat arterial diseases (column 4, lines 35-49). Morishita further teaches that the HGF gene in the method may be appropriately varied depending upon the disease to be treated in a dose 0.0001mg to 100 mg, preferably 0.001mg to 10 mg (column 6, lines 48-54), which anticipates administering at least 50μg of the nucleic acid encoding HGF. Furthermore, Morishita teaches that the dose may be divided into several days or few months, which would anticipate delivering the nucleic acid several times to the subject (column 6, lines 53-54). The pathology of an ischemic disease in a subject results in poor circulation in an affected area (e.g. lower limb, heart, brain) of the subject. HGF gene therapy results in increase circulation of blood in the affected area of the subject. The art of record indicates that there are only a few types of ischemic diseases. Thus, one skilled in the art would have anticipated that

using HGF gene therapy to treat an ischemic disease in a subject taught by Morishita would embrace treating diabetic ischemic disease in the lower limb of a subject with the disease.

In addition, Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section teaches that arteriosclerosis bitterns is a lower limb arteriosclerosis caused by diabetes mellitus resulting in the aggravation in blood circulation followed by lower limb necrosis or gangrene. A scientist, Dr. Ogihara, was cited in the Japan Financial News Paper, Local News Section and he states that, "the HGF has a more potent angiogenesis activity and less side effects than VEGF." Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section further teaches that, "a gene encoding the HGF having angiogenesis activity is introduced into a special circular gene, a plasmid, followed by injection to a muscle around the affected part in the patient." Thus, one of ordinary skill in the art would have been motivated in view of Morishita as obvious over Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) to treat diabetic lower limb ischemic disease in a subject using HGF nucleic acid therapy since diabetic lower limb ischemic disease results in lower limb arteriosclerosis and HGF gene therapy can be used to regenerate new vasculars in an affected of the subject.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the

inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Applicants' arguments with respect to Claims 9, 11, 12, and 14-16 have been considered but are moot in view of the new ground(s) of rejection.

Claims 9, 11, 12, and 15-16 are rejected under 35 U.S.C. 102(e) as anticipated by Isner (US 6,121,246) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) (IDS). Isner teaches a method of treating ischemic tissue in a mammal, which comprises injecting into the tissue a nucleic acid capable of expressing an angiogenic protein, wherein the nucleic acid encodes a hepatocyte growth factor and wherein the amount of nucleic acid injected is 500μg (column 14). Isner teaches that the nucleic acid can be injected at multiple sites throughout the ischemic tissue that would anticipate administering the nucleic acid repeatedly (column 6, lines 27-28). The pathology of an ischemic disease in a subject results in poor circulation in an affected area (e.g. lower limb, heart, brain) of the subject. The art of record indicates that there are only a few types of ischemic diseases. HGF gene therapy results in increase circulation of blood in the affected area of the subject. Thus, one skilled in the art would have anticipated that using HGF gene therapy to treat an ischemic disease in a subject taught by Isner would embrace treating diabetic ischemic disease in the lower limb of a subject with the disease.

In addition, Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section teaches that arteriosclerosis bitterns is a lower limb

arteriosclerosis caused by diabetes mellitus resulting in the aggravation in blood circulation followed by lower limb necrosis or gangrene. A scientist, Dr. Ogihara, is cited in the Japan Financial News Paper, Local News Section and he states that, "the HGF has a more potent angiogenesis activity and less side effects than VEGF." Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section further teaches that, "a gene encoding the HGF having angiogenesis activity is introduced into a special circular gene, a plasmid, followed by injection to a muscle around the affected part in the patient." Thus, one of ordinary skill in the art would have been motivated in view of Isner as obvious over Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) to treat diabetic lower limb ischemic disease in a subject using HGF nucleic acid therapy since diabetic lower limb ischemic disease results in lower limb arteriosclerosis and HGF gene therapy can be used to regenerate new vasculars in an affected of the subject.

Applicants' arguments with respect to Claims 9, 11, 12, and 15-16 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

Applicants' arguments, see paper no.15, filed on 3/4/03, with respect to the provisionally rejection have been fully considered and are persuasive. The provisional rejection of claims 1-8 has been withdrawn because of the cancellation of claims 1-8.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (US 6,121,246) as obvious over Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) (IDS) in view of Afione et al. (IDS, Clin. Pharmacokinet 28: 181-189, 1995). Isner teaches a method of treating ischemic tissue in a mammal, which comprises injecting into the tissue a nucleic acid capable of

expressing an angiogenic protein, wherein the nucleic acid encodes a hepatocyte growth factor and wherein the amount of nucleic acid injected is 500μg (column 14). Isner teaches that the nucleic acid can be injected at multiple sites throughout the ischemic tissue that would anticipate administering the nucleic acid repeatedly (column 6, lines 27-28). The pathology of an ischemic disease in a subject results in poor circulation in an affected area (e.g. lower limb, heart, brain) of the subject. The art of record indicates that there are only a few types of ischemic diseases. HGF gene therapy results in increase circulation of blood in a subject that has an area with poor circulation of blood. In addition, Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section teaches that arteriosclerosis bitterns is a lower limb arteriosclerosis caused by diabetes mellitus resulting in the aggravation in blood circulation followed by lower limb necrosis or gangrene. A scientist, Dr. Ogihara, is cited in the Japan Financial News Paper, Local News Section and he states that, "the HGF has a more potent angiogenesis activity and less side effects than VEGF." Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section further teaches that, "a gene encoding the HGF having angiogenesis activity is introduced into a special circular gene, a plasmid, followed by injection to a muscle around the affected part in the patient." Thus, one skilled in the art would have anticipated that using HGF gene therapy to treat an ischemic disease in a subject taught by Isner would embrace treating diabetic ischemic disease in the lower limb of a subject with the disease. However, Isner does not specifically teach administering the nucleic acid encoding the HGF in the form of HVJ-liposome.

However, at the time the invention was made, HVJ-liposome was known in the art for delivering a nucleic acid to a cell in a mammal as exemplified by Afione. Afione teaches that

HVJ-liposome technology can be used to facilitate nuclear translocation and deter lysosomal degradation (page 185).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to use HVJ-liposome comprising a nucleic acid encoding HGF in a method of treating lower limb diabetic ischemic disease in a subject. One of ordinary skill in the art would have been motivated to use HVJ-liposome to deliver a nucleic acid encoding HGF to a subject because the HVJ-liposome can improve nucleic acid expression by deterring lysosomal degradation of the nucleic acid.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicants' arguments with respect to claims 9 and 14 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Isner et al., US Patent No. 5,980,887 is cited on a PTO-892 because it was attached to the last office action but not listed on the PTO-892.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEDE
PRIMARY EXAMINER